ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jun1399

Persistent Feed Intolerance -Harbinger of Underlying Novel MYH11 Mutation and Visceral Myopathy Type2

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Publication Date: 2025/06/26

Abstract: Feed intolerance is a common clinical concern in preterm neonates. These infants are expected to outgrow this phase but may require varying degrees of pharmacological and non-pharmacological support. In rare cases, feed intolerance may be linked to a surgical condition and could involve an underlying genetic mutation. In such instances, managing these infants poses unique challenges. We report a clinical case of feeding intolerance, congenital hypertrophic pyloric stenosis, intestinal dysmotility, cryptorchidism, and thickened skin in a preterm neonate associated with a novel mutation in the MYH11 gene. This preterm infant presented with feeding intolerance initially attributed to congenital hypertrophic pyloric stenosis. Following surgery, he continued to experience feeding intolerance despite receiving nutrition through a jejunostomy tube, raising concerns about a potential functional obstruction. This intestinal dysmotility was genetically confirmed due to a mutation in the myosin heavy chain (MYH11 gene).

Keywords: *Feed Intolerance, MYH11 Gene, Chronic Intestinal Pseudoobstruction, Intestinal Dysmotility.*

How to Cite: Arpita Roy Ghatak; Abhishek S Aradhya; Venugopal Reddy I; Vedarth Dash; Vuppu Dinesh Kumar (2025) Persistent Feed Intolerance -Harbinger of Underlying Novel MYH11 Mutation and Visceral Myopathy Type2. *International Journal of Innovative Science and Research Technology*, 10(6), 1900-1902. https://doi.org/10.38124/ijisrt/25jun1399

I. INTRODUCTION

Visceral myopathy-2 (VSCM2) is characterised by gastrointestinal symptoms stemming from intestinal dysmotility, including abdominal distention, pain, and vomiting. The clinical presentation may vary from predominantly esophageal symptoms, such as severe reflux that leads to esophagitis and stricture, to chronic intestinal pseudo-obstruction. Bladder involvement resulting in megacystis and megaureter has also been observed and may be evident at birth (1-3). The history of visceral myopathy dates back to 1988 when Scheffler et al. identified the symptoms in four infants, symptomatic by the third week of life (4). Here, we report an Indian neonate diagnosed with visceral myopathy type 2, with a heterozygous mutation in the MYH11 gene.

II. CASE REPORT

A preterm baby born at 30 weeks gestational age from a non-consanguineous marriage was admitted. An unusual skin thickening and cryptorchidism were observed at birth. Orogastric feeds that began on day 2 of life were gradually increased. However, on day 6, further attempts to augment the feeds were unsuccessful due to recurrent vomiting. He was kept Nil per oral on day 9, and empirical antibiotics were initiated for suspected sepsis. Blood cultures later returned negative. Sonography and abdominal radiographs did not indicate Necrotising Enterocolitis (NEC). Feeds were reinitiated on day 13, but strategies such as continuous infusion feeds, prokinetics, and feed thickeners proved ineffective.

On day 24, an upper GI contrast study suggested a gastric outlet obstruction. The baby was found to have hypertrophic pyloric stenosis during the operation, for which Ramstedt's pyloromyotomy and feeding jejunostomy were

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performed. In the postoperative period, jejunal feeds were restarted on day 4; however, nasogastric aspirates reached as high as 50%. Supportive measures, including prokinetics and upright positioning, proved ineffective. A radiological examination ruled out feeding tube malposition. The baby was maintained on parenteral nutrition. Serial blood cultures returned negative results. The baby's unusual skin thickening complicated vascular access. Initially, umbilical lines were utilised to maintain access, but multiple attempts to secure Peripherally Inserted Central Catheter (PICC) lines failed and required a femoral cutdown for IV access.

III. DISCUSSION

Visceral myopathies are includes conditions ranging from chronic intestinal pseudo-obstruction (CIPO) with severe gastrointestinal dysmotility to megacystis-microcolon-intestinal-hypoperistalsis syndrome (MMIHS), which features dysfunctional gastrointestinal (GI) and genitourinary (GU) tracts, impaired colonic growth, and severe early presentation associated with worse outcomes (5). The familial forms of visceral myopathy exhibit phenotype discordance among family members (6).

Around 44-50% of CIPOs are caused by dominant mutations in the smooth muscle actin gene (ACTG2). The rest are caused by other X-linked/recessive genes like MYLK, RAD21, LMOD1, LYL9, and FLNA. Both the ACTG2 (type 1) (7) and MYH11 (type 2) genes have been implicated in visceral myopathies and have been labelled as type 1 (ACTG2 mutation) and type 2 (MYH11 mutation) (8). Dong et al. (1) identified defects in the myosin-heavy chain causing CIPO in a family with seven affected individuals who required long-term parenteral nutrition and/or catheterization.

VSCM2 results from a heterozygous mutation in the MYH11 gene (160745) located on chromosome 16p13. As in any heterozygous mutation, a single abnormal gene inherited from one of the parents is sufficient to cause the disease (2-3). Mutations in MYH11 have been linked to 1% of thoracic aortic aneurysm/dissection cases (9-11). Pathogenic variants identified include missense, splice site, nonsense, and deletion variants occurring in both the motor and coiled-coil-tailed domains of the MYH11 gene (11-13).

Gilbert et al. (2) reported 2 unrelated families with an autosomal dominant mutation in the MYH11 gene linked to dysmotility. In family 1, one of five family members experienced recurrent NEC. Exome sequencing identified a novel heterozygous two-base pair mutation in the MYH11 gene, absent in unaffected family members. In family 2, which included three generations with chronic intestinal dysmotility disorders, two of three heterozygous variants were identified in the MYH11 gene.

The Whole Exome Sequencing (WES) of the index patient revealed a missense mutation at exon 17, [NM_002474.3: c.2063 G>C (p.Gly 688 Ala)]. Testing of the parents via WES has been advised, and genetic counselling has been done for future pregnancies, although there was no similar family history in the last three generations. Given this information and the fact that the patient is heterozygous, the mutation appears to be de novo. The skin finding observed in the index child was novel despite a literature search for mutations associated with the gene. We presume this is due to the abnormality in the smooth muscle of the skin.

The presence of skin abnormalities, cryptorchidism, and congenital hypertrophic pyloric stenosis raised suspicion of genetic involvement, and whole exome sequencing was sent and analyzed by Next-Generation Sequencing. Genetic reports revealed defects in the myosin heavy chain gene (MYH11), which aligned phenotypically with dysmotility. Due to concerns regarding dysmotility and poor long-term outcomes, the parents decided to take the baby home on day 52 of life.

A retrospective study on 160 infants undergoing pyloromyotomy showed 3.8% (n=6) experienced vomiting beyond 72 hours, and half of these resolved within a week. In contrast, 33% (n=2) exhibited severe gastroesophageal reflux disease (GERD), which responded to medical management. Only 16.6% (n=1) required repeat surgery due to incomplete myotomy (14). The gastrojejunostomy performed in the index case did not respond to anti-reflux measures. The possibility of lower atresias was ruled out before the placement of the GJ tube. Abdominal radiographs taken post-op on days 1, 16, and 28 for a non-functioning jejunal tube ruled out displacement, breakage, coiling, and blockage of the tube, attributing the dysmotility to the presence of nearly 50% milky aspirates.

The European Forum on Visceral Myopathy 2022 meeting described the success of gastrojejunal feeds, weight gain achieved with Medium Chain Triglyceride (MCT) Oil, and a handful of cases managed with intestinal transplantation (15). In the index case, intestinal transplantation was probably the next best care option.

IV. CONCLUSION

Visceral myopathy type 2 is a rare differential diagnosis for neonatal feeding intolerance and a reason for failed gastrojejunostomy. Chronic intestinal pseudo-obstruction has a genetic etiology in nearly half of the cases. We report this case to catalog the clinical picture associated with this specific novel mutation.

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